LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Avaxim Junior
hepatitis A virus, inactivated antigen

SE/H/1880/02/DC
2019-1348

This module reflects the scientific discussion for the approval of Avaxim Junior. The procedure was finalised on 2020-11-27. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Sanofi Pasteur has applied for a marketing authorisation for Avaxim Junior, 80 U, suspension for injection, pre-filled syringe. The active substance Inactivated hepatitis A virus (GBM STRAIN) is the same as in Avaxim 160U, Suspension for injection in pre-filled syringe, marketed by Sanofi Pasteur since 1997.

No Public Assessment Report was published after the approval of the original product Avaxim 160 U.

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation has been granted pursuant to Article 8(3) of Directive 2001/83/EC.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Avaxim is approved in Sweden for immunisation of adults since 1997 and for the paediatric population and is now licensed in several countries in the EU. With the exception of the antigen and adjuvant contents, that are 2-fold lower, the paediatric Hepatitis A vaccine formulation is similar to the adult Hepatitis A vaccine formulation, with no novel excipient or process residue. Therefore, it is considered that any nonclinical study conducted with the adult dosage formulation (160 EU/dose) is supportive of the paediatric dosage formulation (80 EU/dose), and no new non-clinical studies have

been submitted by the applicant. The clinical safety profile to the paediatric population is thus well known.

III.1 Ecotoxicity/environmental risk assessment

Vaccines are exempted from requirement to provide environmental risk assessments due to the nature of their constituents. Any waste material from the injection procedure will be taken care of by the health care personnel in accordance to local requirements.

IV. CLINICAL ASPECTS

IV.1 Introduction

Hepatitis A remains a health concern. Based on an ongoing reassessment of the global burden of hepatitis A, preliminary WHO estimates suggest an increase in the number of acute hepatitis A cases from 177 million in 1990 to 212 million in 2005 and increase in the number of deaths due to hepatitis A from 30 283 in 1990 to 35 245 in 2005. More recent Global Burden of Disease studies suggest 159 million yearly new acute hepatitis A cases associated with 15 000 deaths. In addition to the burden observed in countries of high and intermediate endemicity, recent outbreaks within at risk groups (people experiencing homelessness and/or using illicit drugs in settings of limited sanitation) in countries with very low hepatitis A endemicity such as Europe and United States are highlighting the need of prevention plans.
Vaccination against hepatitis A should be part of a comprehensive plan for the prevention and control of viral hepatitis, including measures to improve hygiene and sanitation and measures for outbreak control.

There is no specific treatment for hepatitis A. Several injectable inactivated hepatitis A vaccines are available internationally. All are similar in terms of how well they protect people from the virus and their side-effects. No vaccine is licensed for children younger than 1 year of age.

IV.2 Pharmacokinetics

Not applicable.

IV.3 Pharmacodynamics

The protective efficacy afforded by the Pediatric Hepatitis A vaccine was assessed during the clinical development through the measurement of serum anti-HAV antibodies induced after vaccine injections. The serological results were expressed in terms of geometric mean of anti-HAV titer (anti-HAV GMT) in mIU/mL of serum. The seroprotection lower limit for inactivated hepatitis A vaccines has been historically defined as 20 mIU/mL with the RIA assays and was considered for seroconversion and seroprotection threshold in most of the studies. The absolute lower limit of antibody needed to prevent HAV infection has not been determined. Anti-HAV concentrations are measured in comparison to the immunoglobulin reagent of reference from World Health Organization (WHO) and are expressed in milli-International Units per milliliter (mIU/mL). Concentrations of 10 to 20 mIU/mL, achieved about 1 to 2 months after administration of immunoglobulins, are known to protect against hepatitis A.

IV.4 Clinical efficacy

The Avaxim (80U) clinical development program was comprehensive. The immunogenicity was studied in 9 studies including children at age 1-15 years. The results from five of these studies were pooled. Immunogenicity results from 2918 subjects were presented. Most of the studies were single arm open label studies investigating immune response. Blinding was used when more than one arm was included into studies. The protective efficacy afforded by the Pediatric Hepatitis A vaccine was assessed during the clinical development through the measurement of serum anti-HAV antibodies induced after vaccine injections.

Immunogenicity results obtained through the clinical studies of the Pediatric Hepatitis A vaccine demonstrated that 2 doses given at least 6 months apart induced a protective immune response in all subjects, regardless of their age, HAV serostatus before vaccination and the endemicity level of the region they are living. In an environment of intermediate endemicity, it was also demonstrated that subjects were still seroprotected 7 years after 1 dose of Pediatric Hepatitis A vaccine and based on predictive statistical models, anti-HAV antibody could persist for 20 to 30 years after the recommended 2-doses schedule.
The studies with concomitant administration of Avaxim (80U) simultaneously with some other childhood vaccines showed acceptable Hep A antibody level in this case. Interchangeability studies showed, that when vaccination has been started with another Hep A vaccine, it is acceptable to continue Avaxim (80U) as a second or booster dose in terms of antibody levels.
The effectiveness study in Belarus demonstrated that Avaxim (80U) was stopping successfully Hep A epidemy among children.

Therefore, we can conclude that Avaxim (80U) is highly immunogenic and effective to prevent Hep A infection among children 1-15 year of age.

IV.5 Clinical safety

The applicant presented safety data based on a sufficiently large integrated safety pool (5458 subjects) and a large post marketing treatment pool, which allows a reliable safety evaluation.

The vaccine appears to be overall well tolerable for children with local injection sites, gastrointestinal symptoms, myalgia and arthralgia as main occurring safety events. Safety data collected during the clinical development of the Pediatric Hepatitis A vaccine were consistent across studies, showing reactions known from the use in adults. This vaccine is safe to be used in a two-dose regimen with a decreased reactogenicity after the second dose. No related deaths were reported in the presented clinical development program. Interaction studies with other vaccines showed a higher reactogenicity in combination with MMR vaccine, but an overall acceptable safety profile.

The post marketing experience is extensive with only a small amount of post marketing side effect reports retrieved in a time interval of 17 years. To mention are a very few cases of (fever related) convulsions, which have been included in the SmPC, section 4.8, syncope, which is as “vasovagal syncope” already listed in SmPC section 4.8., isolated (reversible) transaminase elevations of mild nature and anaphylactic reactions seen during the trial program and/or post marketing. Anaphylactic reactions have been now as well listed in the SmPC 4.8. (Auto) immune events have been hardly seen in the presented development program and in the post marketing phase and no safety concern is raised here based on a systematic analysis provided by the company. The vaccine is suggested to be monitored by routine PV activities which is endorsed.

IV.6 Risk Management Plans

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Avaxim.

Safety specification

Table 1: Summary of safety concerns

Important identified risks	None
Important potential risks	None
Missing information	• Data in pregnant and lactating women (1) (2) (3) (4) (5) • Data in immuno-compromised patients. • Data in patients with chronic liver diseases

Pharmacovigilance Plan

Table 1: Important risks

Areas requiring confirmation or further investigation	Proposed routine and additional PV activities	Objectives
None	Not applicable	Not applicable

Table 2: Missing information

Areas requiring confirmation or further investigation	Proposed routine and additional PV activities	Objectives
Data in pregnant and lactating women	Routine Pharmacovigilance including signal detection	Comprehensive evaluation in Periodic Benefit Risk Evalution Report (PBRER) Obtain qualitative data on exposure during pregnancy Update the Summary of Product Characteristics (SmPC) in a timely manner
Data in immuno-compromised patients	Routine Pharmacovigilance including signal detection	Comprehensive evaluation in PBRER Update the SmPC in a timely manner
Data in patients with chronic liver diseases	Routine Pharmacovigilance including signal detection	Comprehensive evaluation in PBRER Update the SmPC in a timely manner

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP

The submitted Risk Management Plan, version 2.0 signed 06/Nov/2017 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

IV.7 Discussion on the clinical aspects

The extensive clinical and post-marketing experience with the Pediatric Hepatitis A is considered to have demonstrated the prophylactic value of the vaccine. The safety profile of the Pediatric Hepatitis A vaccine is comparable to that of other products in this therapeutic class. Based upon this review of the data, no new safety concerns have been identified during the current reporting interval. The benefit-risk for the Pediatric Hepatitis A vaccine remains positive when used as described in the current reference safety information.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The extensive clinical and post-marketing experience with the Pediatric Hepatitis A is considered to have demonstrated the prophylactic value of the vaccine. The safety profile of the Pediatric Hepatitis A vaccine is comparable to that of other products in this therapeutic class. Based upon this review of the data, no new safety concerns have been identified during the current reporting interval. The benefit-risk for the Pediatric Hepatitis A vaccine remains positive when used as described in the current reference safety information.

The benefit/risk ratio is considered positive and Avaxim Junior, 80 U, suspension for injection, pre-filled syringe is recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Avaxim Junior, 80 U, suspension for injection, pre-filled syringe was positively finalised on 2020-11-27.

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SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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